DEPARTMENT OF HEALTH AND HUMAN SERVICES

Statement by

Dr. Neal Nathanson
Director, Office of AIDS Research

on
Fiscal Year 2001 President's Budget Request
for the National Institutes of Health

Mr. Chairman and Members of the Committee:

I am pleased to present the President's budget request for the AIDS research programs of the NIH for Fiscal Year 2001, a sum of $2,111.2 million, an increase of $105.0 million above the comparable FY 2000 appropriation. The NIH budget request includes the performance information required by the Government Performance and Results Act (GPRA) of 1993. Prominent in the performance data is NIH's first performance report which compares our FY 1999 results to the goals in our FY 1999 performance plan. As our performance measures mature and performance trends emerge, the GPRA data will serve as indicators to support the identification of strategies and objectives to continuously improve programs across the NIH and the Department.

The Office of AIDS Research (OAR) sets the scientific agenda for the large and diverse NIH AIDS research program. To this end, we develop the annual comprehensive AIDS research plan and budget, based on the most compelling scientific priorities that will lead to better therapies and prevention for HIV infection and AIDS. Those priorities are determined through a collaborative process involving the NIH institutes and non-government experts from academia and industry, with the full participation of AIDS community representatives.

Mr. Chairman, at our hearings last year, you and other members of the subcommittee expressed tremendous support for research to address the international dimension of the AIDS epidemic. That support was a catalyst for efforts that have increased throughout the year. In January, the United Nations Security Council declared

that AIDS has become an issue of national security, representing a new kind of threat to political stability. AIDS in Africa is killing ten times as many people as war, sabotaging economic development, leading to massive social breakdown, and creating a generation of orphans. Ambassador Richard Holbrooke called AIDS "a direct, cancerous growth on the political, social, and economic security of Africa."

THE UNRELENTING PANDEMIC

By every definition, AIDS is the great plague of the 20th century – an epidemic of biblical proportions (Chart 1). AIDS already has killed more than 16 million people, surpassing tuberculosis and malaria as the leading infectious cause of death worldwide, according to recent data from the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO). In 1999, a record 2.6 million people died from AIDS -- more than in any prior year. UNAIDS estimates that in India between 3 and 5 million people are infected, with new infections doubling every 14 months. New epidemics are rapidly increasing in Russia, Eastern Europe, and in China. AIDS remains a serious threat in Latin America and the Caribbean. Africa (Chart 2) remains the epicenter of the pandemic, bearing the largest disease burden, with 70 percent of people living with AIDS worldwide, 83 percent of global AIDS deaths, and 95 percent of the world's AIDS orphans. HIV-infected women aged 15 to 49 outnumber infected men. In Harare, the capital of Zimbabwe, 40 percent of adults are HIV-infected. Cemeteries are filled and morgues are open 24 hours a day. The impact of AIDS on developing nations and many former communist countries is staggering, with even greater potential disaster to come. AIDS is reversing decades of progress from important public health efforts, lowering life expectancy, and significantly affecting international businesses. Lost productivity and profitability, the cost of sickness and death benefits, and the decline in a skilled workforce in the developing world will have economic effects worldwide. AIDS is affecting the military capabilities of some countries as well as the international peacekeeping forces.

THE EVOLVING EPIDEMIC IN THE UNITED STATES

In the U.S., the incidence of new AIDS cases has declined, due largely to expanded use of new antiretroviral therapies that prevent progression of HIV infection to AIDS, but the state of Illinois just announced a 24% increase in AIDS cases in 1999. The previous decline in death rates has now leveled off. Most significantly, the annual incidence of new HIV infections has not declined since 1990 (Chart 3). This means that although therapeutic interventions are delaying death -- at least for a time -- we have not slowed the epidemic. Chart 4 shows that HIV infection rates are continuing to climb in two major groups – women and minority populations. AIDS affects the disenfranchised in our society -- the poor, the homeless, and those with addictive or mental disorders. Rates are also increasing in young homosexual men and people over 50 years of age. Further, drug resistant strains of HIV present a serious public health concern.

These data forebode an epidemic of even greater magnitude ahead, and shape our most urgent research priorities. These priorities address two critical populations – those living in developing countries, and the minority populations of the U.S.-- with a two-pronged agenda: therapeutic research to treat those who are already infected; and prevention research to reduce HIV transmission. Our prevention agenda includes both vaccine and non-vaccine strategies, such as behavioral research, development of topical microbicides, and prevention of perinatal transmission.

PRIORITY: INTERNATIONAL RESEARCH

As more than 90 percent of new infections occur in developing countries, where current therapeutic interventions are unaffordable and undeliverable, NIH is increasing our international AIDS research portfolio and pursuing interventions that can be implemented in these resource- and infrastructure-deprived nations. I will cite just a few examples. A recent NIAID-sponsored clinical trial in Uganda demonstrated that nevirapine, an antiretroviral drug costing less than $4, given once to the mother and once to the baby at birth, could reduce mother-to-child transmission by 50%. The NIH

vaccine research effort underscores the crucial role of NIH in addressing prevention needs worldwide. Clinical trials within both the new NIAID Vaccine Trials Network and Prevention Trials Network are expected to involve international sites. The OAR is supporting the first international conference on microbicides to stimulate new research initiatives in this critical area. To further our efforts and enhance international collaboration, the Fogarty International Center is expanding its research and training programs in many developing nations. The OAR FY 2002 annual plan, which we are now developing, includes a special section for international research, and we have established an International AIDS Research Collaborating Committee to bring together all of the Departments of the U.S. government conducting AIDS research, along with international partners such as the UNAIDS and the World Bank.

PRIORITY: HEALTH DISPARITIES IN THE U.S.

The disproportionate impact of the HIV/AIDS epidemic on U.S. minority communities is demonstrated graphically on Chart 5. AIDS remains the number one cause of death among young African American men. OAR has established the Ad Hoc Working Group on Minority Research to advise us on the scientific priorities in this critical research area, and we have added a new section on research targeting minorities to our plan. We are directing increased resources toward new interventions that will have the greatest impact on these groups. These include interventions that address the co-occurrence of other STDs, hepatitis, drug abuse, and mental illness; and interventions that consider the role of culture, family, and other social factors in the transmission and prevention of these disorders in minority communities. NIH is making significant investments to improve research infrastructure and training opportunities for minorities, and we will continue to assure the participation of minority subjects in AIDS clinical trials as well as in natural history, epidemiologic, and prevention studies. In response to the Congressional Black Caucus initiative, the OAR has provided additional funds to projects aimed at: increasing the number of minority investigators conducting behavioral and clinical research; targeting the links between substance abuse, sexual behaviors and

HIV infection; increasing outreach education programs targeting minority physicians and at-risk populations; and expanding our portfolio of population-based research. We estimate that with this budget request, NIH will devote approximately $427 million to research targeting AIDS in minority communities.

PRIORITY: BETTER THERAPIES

The development of protease inhibitors has had a significant impact on the length and quality of life for many HIV-infected people in the US. However, at the recent scientific meeting on retroviruses, the overriding theme was the long and serious list of problems for patients receiving these HIV therapies, including: 1) failure to obtain a satisfactory reduction in viral load even for patients who comply with treatment regimens; 2) expensive and complicated regimens that make compliance difficult; 3) drug toxicities; 4) metabolic and cardiac complications, including diabetes; and 5) drug resistance. We must develop and test new, simpler, less toxic, and cheaper anti-HIV drugs. Chart 6 summarizes our key priorities to accomplish that goal: 1) develop new targets for the design of new antiviral drugs; 2) conduct clinical trials to answer key questions such as: At what point in the disease process should therapy be initiated and which combination of drugs should be used? At what point should the drugs be switched and to which drugs? How can toxicities and drug resistance be prevented? How can regimens be simplified and compliance improved? and 3) translate research results into clinical practice information that is useful to caregivers and their patients, particularly in minority communities.

PRIORITY: HIV PREVENTION

NIH supports a comprehensive approach to HIV prevention research that includes contributions from the biomedical, behavioral, and social sciences. The OAR prevention science research agenda (Chart 7) targets interventions to both infected and uninfected at-risk individuals to reduce HIV transmission. In addition, different strategies must be applied to each subepidemic in the US and around the world. Our

biomedical prevention research priorities include areas such as the development of topical microbicides for women; perinatal prevention strategies, including understanding of breast-feeding risk; and management of sexually transmitted diseases that enhance risk of HIV transmission. NIH also supports behavioral research strategies, including prevention interventions related to drug and alcohol use. We are focusing on interventions targeting both HIV-infected individuals who may not know their HIV status and HIV-infected individuals who are successfully responding to therapy. Data suggest that some of these individuals may believe that they are less infectious or that they cannot be reinfected, and thus they may re-engage in risky behaviors.

PRIORITY: VACCINES

A safe and effective vaccine is the critical missing element in our armamentarium. In 1997, the President challenged the nation to develop an AIDS vaccine. Consistent with this challenge, NIH has moved forward aggressively to build a comprehensive vaccine research enterprise. Funds in this request represent more than a 100 percent increase in NIH vaccine research since FY 1997. These funds will provide new grants to foster innovative HIV vaccine research and allow the invigoration and reorganization of the NIH vaccine clinical trials effort. The new Dale and Betty Bumpers Vaccine Research Center will be occupied this summer. Dr. David Baltimore continues to chair the AIDS Vaccine Research Committee which advises the NIH on the overall vaccine program. In February 1999, NIH-supported investigators initiated the first AIDS vaccine trial in Africa. In collaboration with industry partners, NIH has now tested 28 different HIV vaccine candidates, individually or in combinations, in over 3000 uninfected volunteers. Several new vaccines, including vaccines designed to induce mucosal immunity, novel DNA vaccines, and more complex vaccines presenting several viral proteins, have entered phase I trials. In addition, recent studies of “therapeutic vaccines” that do not prevent infection, but can prevent or delay disease progression in animal models have offered opportunities for additional vaccine strategies.

Significant incremental advances have been made in the development of an AIDS vaccine. A number of candidate vaccines have been formulated for use in rhesus monkeys where they can be tested for their ability to protect against a "challenge" with a simian immunodeficiency virus that has been shown to produce AIDS in these animals. This permits the rapid testing of the potential protective efficacy of vaccine concepts. Chart 8 shows the blood levels of two groups of monkeys, one vaccinated and one given a placebo control. The vaccinated monkeys had a much reduced infection, with a far better survival than the control group. Protection of this magnitude has been seen with several candidate vaccines. In another recent study, two versions of the same vaccine were tested in humans for their ability to produce immune responses. Both versions of the vaccine induced the production of antibodies and cellular immune responses (CTLs), but only in a proportion of immunized subjects. This was not a trial of effectiveness, however the subjects were followed for HIV infections. There appeared to be about half as many infections in the immunized subjects, although the numbers were too small to be statistically significant. Results of this kind are encouraging and lead us to hope that full scale trials of vaccine effectiveness may begin in humans in the next few years.

BENEFITS TO OTHER DISEASE RESEARCH

AIDS research is unraveling the mysteries surrounding many other infectious, malignant, neurologic, autoimmune and metabolic diseases. AIDS research has provided an entirely new paradigm for drug design and development to treat viral infections. One example this year was the development of the new flu drug, Relenza, which directly benefitted from AIDS research. The drug known as 3TC, developed to treat AIDS, is now the most effective therapy for chronic hepatitis B infection. Drugs developed to prevent and treat AIDS-associated opportunistic infections also provide benefit to patients undergoing cancer chemotherapy or receiving anti-transplant rejection therapy. AIDS is also providing new understanding of the relationship between viruses and cancer.

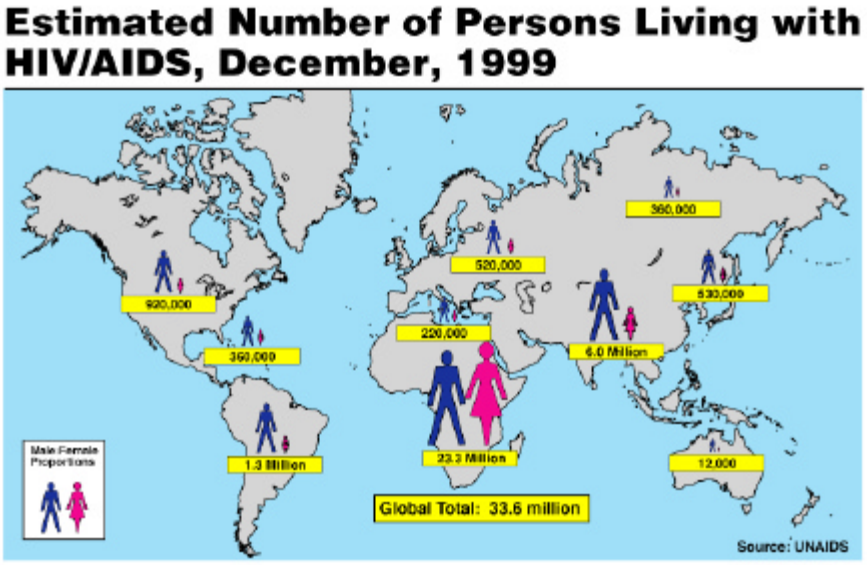
SUMMARY

The transmissible nature of HIV--between individuals and across borders and populations--makes it radically different from non-transmissible diseases such as heart disease and cancer. There is the potential for unlimited spread, and also the possibility for a dramatic reduction in new infections--and thus ultimate control of the pandemic--in a way that can never be possible for noninfectious diseases. The impact of an intervention that reduces the probability of transmission, breaking the link in the epidemic chain, extends far beyond the treated or protected individual.

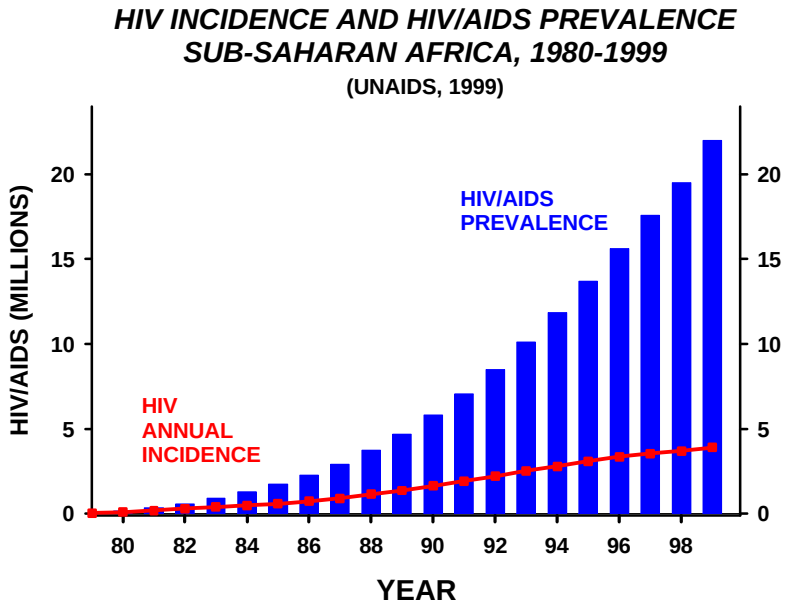
We have made enormous strides in our fight against this horrible disease, but these were only small skirmishes in a major global war. As this Committee clearly recognizes, our progress will be meaningless unless we can make the benefits of our research findings available to populations desperately in need both here in our own country and around the world. The worldwide human and economic toll of this insidious disease is profound, and we will never solve the problem of AIDS for our own citizens without controlling the epidemic in the rest of the global village. We cannot afford to leave anyone behind.

We are deeply grateful to the Committee for your steadfast support. I would be pleased to respond to any questions you may have.

1

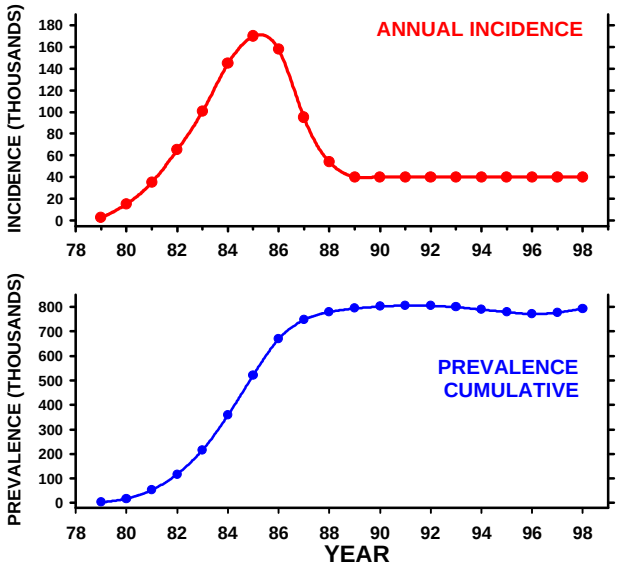

Estimated Number of Persons Living with HIV/AIDS, December, 1999
920,000
360,000
1.3 Million
520,000
220,000
23.3 Million
360,000
530,000
6.0 Million
12,000
Male Female Proportions
Global Total: 33.6 million
Source: UNAIDS

2


HIV INCIDENCE AND HIV/AIDS PREVALENCE
SUB-SAHARAN AFRICA, 1980-1999
(UNAIDS, 1999)
HIV/AIDS (MILLIONS)
HIV/AIDS PREVALENCE
HIV ANNUAL INCIDENCE
0
5
10
15
20
80
82
84
86
88
90
92
94
96
98
YEAR

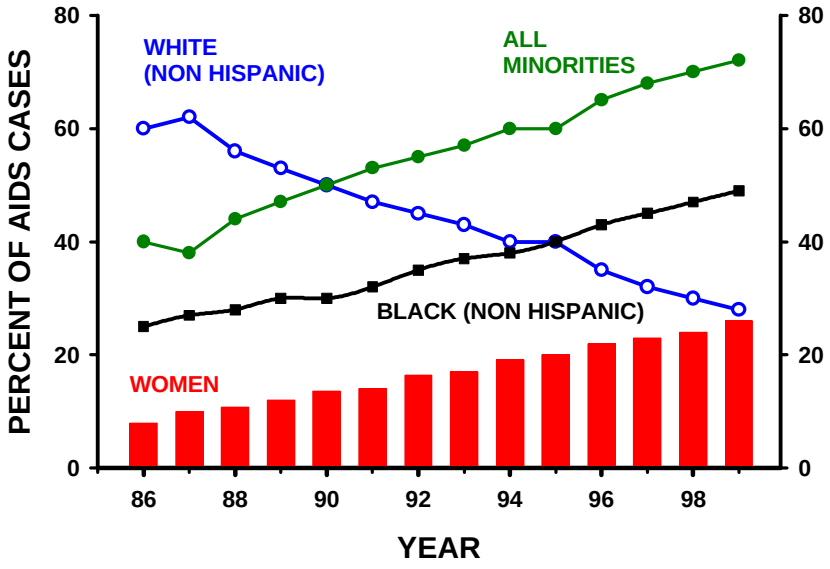
3

INCIDENCE AND PREVALENCE OF HIV/AIDS
USA, 1979-1998
(ROSENBERG ET AL, 1998, BASED ON CDC DATA)



4

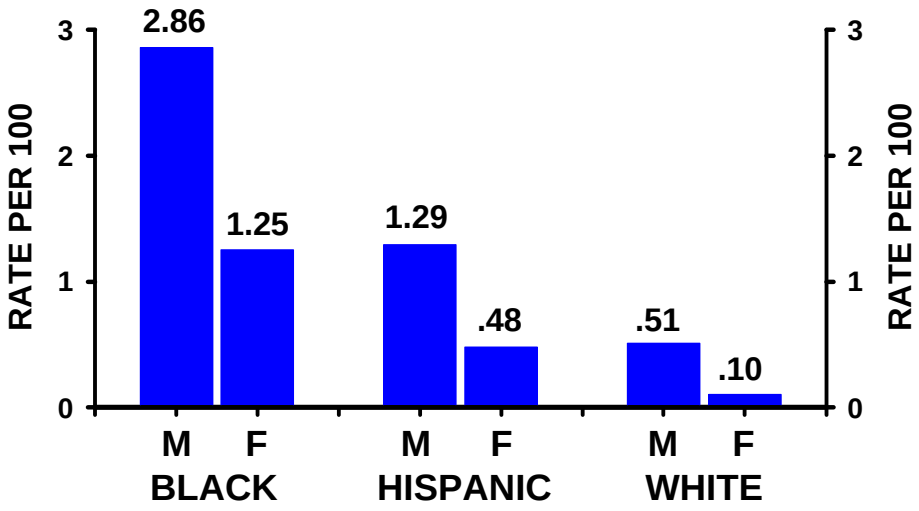
AIDS INCIDENCE BY RACE AND SEX
USA, 1986-1999 (CDC)



5

ANNUAL HIV INFECTION RATE PER 100 PERSONS BY RACE AND ETHNICITY, AGES 23-27 UNITED STATES, 1993

(Rosenberg et al, JAMA, 1998, 279: 1894)



6

AIDS THERAPY

DRUG DISCOVERY AND CLINICAL TRIALS

1

DRUG DISCOVERY
- new targets

2

CLINICAL TRIALS
- when to start, what to select
- when to switch, what to select
- side effects, resistance, compliance

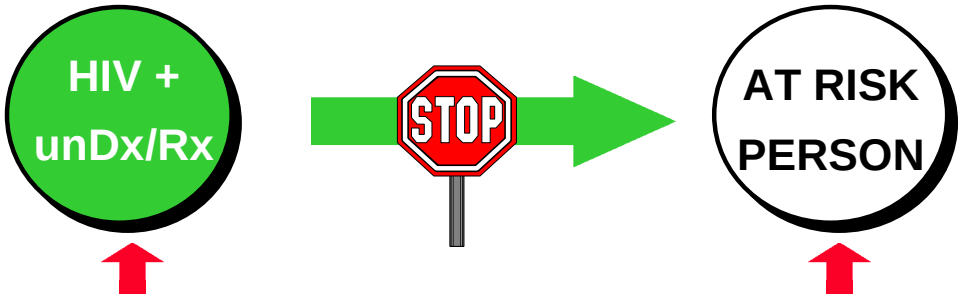
3

TRANSLATION, DISSEMINATION
- access to services
- disparities in quality of care
- minority outreach, training

7

HIV/AIDS PREVENTION

INTERVENTION RESEARCH PRIORITIES



- HAART
- PERINATAL INTERVENTION
- SAFER SEX PRACTICES
- REDUCE IDU TRANSMISSION
- MANAGEMENT STDs

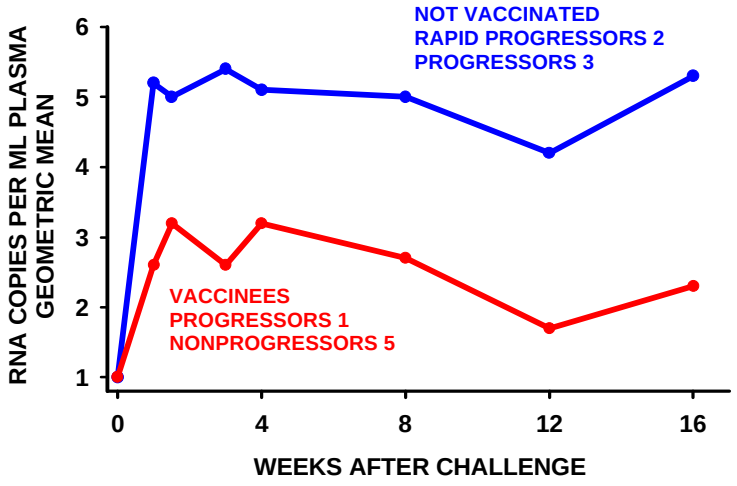
- MICROBICIDES
- VACCINE
- SAFER SEX PRACTICES
- REDUCE IDU TRANSMISSION
- MANAGEMENT STDs

8

AIDS VACCINE

PROTECTION OF RHESUS MACAQUES

(Ourmanov et al, J Virology, 2000 in press)



Dr. Neal Nathanson

Biographical Summary

Dr. Nathanson was appointed Director of the Office of AIDS Research (OAR) at the National Institutes of Health in May, 1998. OAR is responsible for coordinating the scientific, budgetary, legislative, and policy elements of the NIH AIDS research programs, as well as for promoting collaborative research activities in domestic and international settings.

Dr. Nathanson has a broad background in virology, epidemiology, and public health. He has served on a number of government advisory groups, including the NIH AIDS Vaccine Research Committee, the UNAIDS Vaccine Advisory Committee, and consultant to the Center for Biologics Evaluation and Research/U.S. Food and Drug Administration Vaccines and Related Biological Products Advisory Committee.

Dr. Nathanson was educated at Harvard University, where he received both a BS and an MD degree, followed by clinical training in internal medicine at the University of Chicago and postdoctoral training in virology at Johns Hopkins University. Early in his career, Dr. Nathanson spent two years at the Centers for Disease Control where he headed the Polio Surveillance Unit. Later he joined the faculty of the Johns Hopkins School of Hygiene and Public Health where he became Professor and head of the Division of Infectious Diseases in the Department of Epidemiology. He then moved to the University of Pennsylvania Medical Center where he chaired the Department of Microbiology for 15 years, finally serving for two years as Vice Dean for Research and Research Training.

Dr. Nathanson is known particularly for his contributions to the field of viral pathogenesis and epidemiology as the author of the definitive papers on the epidemiology of polio. During a research career spanning 35 years, he has worked with a large number of viruses and disease conditions, and has made many important contributions such as the clear delineation of the two major routes by which poliovirus could be disseminated in its host, the introduction of immunosuppression to understand the role of the immune response in recovery from primary viral infections, the demonstration that lymphocytic choriomeningitis could be prevented or enhanced by immune manipulation, and the detailed genetic analysis of bunyavirus virulence. He did some of the early studies of visna virus of sheep, the prototype of the lentiviruses, of which the AIDS virus is another member. In recent years, his NIH-sponsored work included studies of the mechanisms by which HIV causes disease.